REMARKS

Upon entry of the present amendments, claims 1,4, 6-16 and 29-34 are pending. Claims 24-28 are cancelled by the present amendment. The specification was amended to delete computer program listing "Appendix I" at pages 30-67 and submit it on a compact disc. The specification was further amended to insert an appropriate reference to the newly-added computer program listing appendix on compact disc.

The foregoing amendment is made without any intention to abandon the subject matter of the specification and the claims as filed December 5, 2003, but with the intention that claims of the same, lesser or greater scope may be pursued in the present application or in a continuation, continuation-in-part, or divisional application. Applicant believes that the present amendment does not add new matter.

The bases for the Examiner's rejections in the April 17, 2006 Office Action are addressed in turn below.

Specification – Computer Program Listing

As required at page 3 of the April 17, 2006 Office Action, Applicants have cancelled the computer program listing appearing in the specification on pages 30-67, filed a computer program listing appendix on compact disc in compliance with 37 C.F.R. §1.96(c), and inserted an appropriate reference to the newly added computer program listing appendix on compact disc at the beginning of the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

Claim objection – Markush group

Claim 25 was objected to at pages 3-4 of the April 17, 2006 Office Action, and Applicants were requested to insert the word "consisting" between the words "group" and "of".

Claim 25 is cancelled by the present amendment. Accordingly, the objection is moot and Applicants respectfully request reconsideration and withdrawal of this claim objection.

35 U.S.C. §112, 1st paragraph – Enablement requirement

Claims 1, 4, 6-16 and 26-34 are rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. According to the April 17, 2006 Office Action at

pages 4-10, enablement was considered in view of the Wands factors (MPEP 2164.01(A). The rejection is based *inter alia* on the fact that the claims are broad in that they encompass pharmaceutical compositions comprising at least one modified mRNA encoding any polypeptide that has biological activity or is antigenic and, thus, pharmaceutical compositions for the treatment of any disease or for the vaccination against any infection or cancer. With respect to the guidance of the specification and working examples, the Examiner stated that: "While the specification and working examples teach how to make a modified mRNA that meets the structural characteristics of the claimed invention, the specification does not teach how to use the pharmaceutical compositions for any therapy. No working examples that demonstrate a therapeutic outcome are provided." Office Action at pages 7-8. With respect to the state and predictability of the art, the Examiner stated that: "The use of RNA for vaccination is unpredictable in that the process depends upon cell-specific and tissue-specific efficient transfer of the nucleic acid... Furthermore, the success of nucleic acid vaccination is unpredictable with regard to obtaining a prophylactic or therapeutic effect..." Office Action at pages 8-9. The Examiner concluded that: "In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention." Office Action at page 10.

Applicants traverse. The Examiner's rejection is founded on concerns that the use of RNA for vaccination is unpredictable in that the process depends upon cell-specific and tissue-specific efficient transfer of the nucleic acid and that the Specification provides no working examples that demonstrate a therapeutic outcome. Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Dr. Ingmar Hoerr, one of the inventors of the present application (hereinafter, the "Hoerr Declaration), which describes a series of studies that address the Examiner's concerns. The studies were conducted using methods well known in the art and using the compositions of the claimed invention.

Modified mRNAs were shown to be more efficiently expressed than wild type mRNA both *in vitro* and *in vivo*. For example, when human Peripheral Blood Mononuclear Cells (hPBMCs) were transfected *in vitro* with either modified or wild type mRNA encoding Luciferase, the expression of Luciferase was significantly greater for hPBMCs transfected with modified RNA when compared with the wild type mRNA. See, paragraph 11 of the Hoerr Declaration.

Moreover, when hPBMCs were incubated with either modified or wild type mRNA encoding Influenza A matrix protein M1 (Flu), the modified mRNA induced greater release of both IL-6 and TNFα compared to the wild type mRNA. The release of the cytokines IL-6 and TNFα indicates the induction of an immune response. See, paragraph 14 of the Hoerr Declaration. Similar results were obtained for the transfer of modified mRNA *in vivo*. When expression of Luciferase was measured 24h after intradermal injection of either wild type or modified mRNA coding for Luciferase, modified mRNA resulted in higher expression levels of Luciferase *in vivo* than wild type mRNA. See, paragraph 11 of the Hoerr Declaration. These *in vivo* results are further supported by additional studies described below. Accordingly, Applicants respectfully submit that issues of state and predictability of the art pertaining to wild type mRNA should not be extended to the modified stabilized mRNA compositions of the present invention, as these are efficiently expressed both *in vitro* and *in vivo*.

With respect to examples that demonstrate a therapeutic outcome, the Hoerr Declaration describes numerous *in vivo* studies addressing this concern. As described in paragraphs 7-10 of the Hoerr Declaration, immunization of mice with modified mRNA coding for Ovalbumin led to the formation of Ovalbumin-specific IgG1-antibodies, which indicates a humoral immune response against the antigen Ovalbumin. This resulted in the rejection of the tumor cells and a significant reduction in tumor size, as illustrated in the figures on pages 3-5 of Exhibit B. Mice vaccinated with the wild type mRNA also showed tumor rejection, but to a much lower extend than the mice which were vaccinated with GC-enriched mRNA. This clearly demonstrates that vaccination with a modified mRNA of the present invention coding for an antigen is able to protect mice against tumor cells which express the antigen.

The induction of a CTL immune response was assessed in mice by vaccination with wild type or modified mRNA coding for the viral antigen, Influenza A matrix protein M1 (Flu) and the detection of apoptosis of target cells. As described in paragraphs 12-13 of the Hoerr Declaration, modified mRNA induced a higher CTL response specific against Flu compared to the wild type mRNA. These results indicate that, with modified therapeutic mRNA, more cytotoxic T cells specific for the antigen are present, and are able to fight against cells which express the antigen.

Finally, two studies are described in which a human patient with tumors were injected several times with modified mRNA coding for hepatitis B surface (HBS) antigen, and wild type

mRNA coding for several tumor antigens and viral antigens. *See*, paragraphs 15-19 of the Hoerr Declaration. In both studies, tumor regression was visible in the patients' computer tomography (CT) scans. Moreover, the modified mRNA coding for HBS antigen was additionally used as markers for induction of an immune response because the detection of HBS antibodies is a standard procedure in the clinic. The results indicated that vaccination with modified mRNA coding for tumor antigens and viral antigens can induce antigen-specific antibodies, as indicated by the increase of the titer against the HBS antigen detected in the patient. These two clinical trials indicate that vaccination of tumor patients with mRNA coding for tumor antigens and viral antigens can induce the production of antigen-specific antibodies and induces the immune system to reject the tumor cells. This led to tumor regression in both patients.

In summary, the Hoerr Declaration describes several studies, using various modified, stabilized mRNA coding for several tumor antigens and viral antigens, demonstrating that the modified mRNA are efficiently transferred, both *in vitro* and *in vivo*, and can induce desired therapeutic outcome in animal models, as well as in human patients. Accordingly, Applicants submit that the subject matter of the claims is described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. §102(b) – Chen *et al.* (WO 99/20774)

Claim 24 is rejected under 35 U.S.C. §102(b) as being anticipated by Chen *et al.* (WO 99/20774).

Applicants traverse. In order to expedite allowance of the present application, Applicants cancelled claim 24 in the present amendment. Accordingly, the present ground of rejection is moot and Applicants request reconsideration and withdrawal of this rejection.

The remaining grounds of rejection under 35 U.S.C. §102 and 35 U.S.C. §103 were deemed by the Examiner to be moot in light of the new ground(s) of rejection under 35 U.S.C. §112, 1st paragraph. Accordingly, these ground(s) of rejection are not addressed herein.

CONCLUSION

On the basis of the foregoing amendments, applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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Michel Morency, Ph.D.
Reg. No. 50,183
Attorney for Applicant
Foley & Lardner LLP
111 Huntington Avenue, 26th Floor
Boston, MA 02199
Telephone: 617-342-4000
Facsimile: 617-342-4001